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CHASE J. TROMBELLA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

PHILIPPE POULETTY, ET AL.

Serial No.: TO BE ASSIGNED

Filing Date: HEREWITH

For: **REACTIVELY MODIFIED
THERAPEUTIC COMPOUNDS HAVING AN
EXTENDED LIFETIME IN VIVO (As
Amended)**

Examiner: TO BE ASSIGNED

Group Art Unit: 1641

PRELIMINARY ADMENTMENT

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In advance of prosecution, please enter the following amendments and remarks.

AMENDMENTS

IN THE TITLE

At page 1, line 1, replace the title with --REACTIVELY MODIFIED THERAPEUTIC
COMPOUNDS HAVING AN EXTENDED LIFETIME IN VIVO--

IN THE SPECIFICATION

At page 1, line 4, after "CROSS REFERENCE TO RELATED APPLICATIONS"
replace the paragraph with the following paragraph:

--This application is a Continuation Application of 09/539,766 filed March 31, 2000;
which is a Continuation Application 08/477,900 filed June 7, 1995 now U.S. Patent No.
6,103,233; which is a Continuation Application of 08/237,346 filed May 3, 1994 now US Patent
No. 5,612,034; which is a Continuation-in-Part Application of 08/137,821 filed October 15, 1993
(Abandoned).--

IN THE CLAIMS

Please CANCEL claims 1-12 of the parent case and replace them with the following.

Please ADD the following new claims:

13. (New) A therapeutic compound of the formula: X-Y-Z, wherein X is a therapeutic entity, Y is an *in vivo* cleavable linking entity covalently connecting said therapeutic entity to Z, and Z is a chemically reactive group for reacting *in vivo* with a reactive functionality on an endogenous vascular or blood component protein so as to form a covalent bond therewith, wherein said reactive functionality is selected from the group consisting of amino, carboxylate, and thiol reactive functionalities, said therapeutic agent thereby covalently linking *in vivo* said therapeutic entity to said protein through formation of said covalent bond and whereby said linking entity is cleaved after covalent linking of the therapeutic entity to the protein, thereby releasing the therapeutic entity.

14. (New) A therapeutic compound according to claim 13, wherein said therapeutic entity is a synthetic organic drug.

15. (New) A therapeutic compound according to claim 13, wherein said therapeutic entity is a peptide.

16. (New) A therapeutic compound according to claim 13, wherein said linking entity has from 2-30 atoms in a backbone chain.

17. (New) A therapeutic compound according to claim 13, wherein said linking entity comprises an oligopeptide; an oligonucleotide; a disulfide; an organic divalent group which can be aliphatic, aromatic, alicyclic, heterocyclic or combinations thereof.

18. (New) A therapeutic compound according to claim 13, wherein said chemically reactive group is selected from the group consisting of N-hydroxysuccinimide, carbodiimide anhydride, and N-hydroxysulfosuccinimide.

19. (New) A therapeutic compound according to claim 13, wherein said chemically reactive group is N-hydroxysuccinimide.

20. (New) A therapeutic compound according to claim 13, wherein said chemically reactive group comprises maleimide and said reactive functionality is a thiol group.

cleavable linking entity covalently connecting said therapeutic entity to a chemically reactive group, said chemically reactive group being complementary in reactivity to a reactive functionality of an endogenous blood or vascular system protein of a patient, said reactive functionality being selected from the group consisting of amino, carboxylate, and thiol reactive functionalities; wherein said reactive group reacts *in vivo* with said reactive functionality to form a covalent bond therewith and whereby said compound covalently links *in vivo* said therapeutic entity to said protein through formation of said covalent bond.

27. (New) A composition according to claim 26, wherein said therapeutic entity is a synthetic organic drug.

28. (New) A composition according to claim 26, wherein said therapeutic entity is a peptide.

29. (New) A composition according to claim 26, wherein said chemically reactive group is N-hydroxysuccinimide.

30. (New) A composition according to claim 26, wherein said chemically reactive group comprises maleimide.

31. (New) A composition according to claim 26, wherein said therapeutic entity is a synthetic organic drug; said linking entity is from 6 to 15 atoms in length between said therapeutic entity and said chemically reactive group; and said chemically reactive group is N-hydroxysuccinimide, N-hydroxysulfosuccinimide or maleimide.

32. (New) A composition according to claim 26, wherein said therapeutic entity is a synthetic peptide; said linking entity is from 6 to 15 atoms in length between said therapeutic entity and said chemically reactive group; and said chemically reactive group is N-hydroxysuccinimide, N-hydroxysulfosuccinimide, or maleimide.

33. (New) A method of providing a therapeutic activity to a patient, said method comprising administering to said patient in a therapeutically effective amount a composition according to claim 26.

REMARKS

Claims 1-12 are cancelled. New claims 13-33 are added. New claims 13-33 find support at page 3, lines 7-9 and page 12, lines 6-10 and 15-29 to page 13, line 6.

The specification has been amended to indicate that this application claims priority through a chain of applications back to serial number 08/137,821 filed October 15, 1993.

The Examiner's attention is directed to the Information Disclosure Statement included with the application as filed.

Attached hereto is a marked up version of the changes made to the specification by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

CONCLUSION

Early and favorable action is requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for

any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 500862000105. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: August 3, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

[SUPER-GLOBULINS FOR *IN VIVO* ETENDED LIFETIMES]
REACTIVELY MODIFIED THERAPEUTIC COMPOUNDS HAVING
AN EXTENDED LIFETIME IN VIVO

[This application is a continuation-in-part of application Serial No. 08/137,821, filed October 15, 1993, which application was a continuation-in-part of application Serial No. 08/070,092, filed May 27, 1993, which was a continuation-in-part of application Serial No. 07/592,214, filed October 3, 1990.]

This application is a Continuation Application of 09/539,766 filed March 31, 2000; which is a Continuation Application 08/477,900 filed June 7 1995 now Patent No. 6,103,233; which is a Continuation Application of 08/237,346 filed May 3, 1994 now US Patent No. 5,612,034; which is a Continuation-in-Part Application of 08/137,821 filed October 15, 1993 (Abandoned).

INTRODUCTION

Technical Field

The field of this invention is agent, particularly therapeutic agent, delivery in a mammalian host.

Background

Delivery of therapeutic agents to a mammalian host can frequently be as important as the activity of the drug in providing effective treatment. For the most part, drugs are delivered orally, frequently initially at a dosage below the therapeutic dosage and by repetitive administration of the drug, the dosage is raised to a therapeutic level or a level exceeding the therapeutic level. In many cases, the fact of having a dosage above therapeutic level provides for adverse effects, since most drugs are not only